

**Practitioner's Docket No. 701586-050174-DIV****PATENT****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Adam Lerner  
Serial No.: 10/060,759 Group: 1614  
Filed: January 30, 2002 Examiner: James D. Anderson  
Confirmation No.: 8480 Customer No.: 50607  
For: COMPOSITIONS AND METHODS FOR THE TREATMENT OF  
CHRONIC LYMPHOCYTIC LEUKEMIA

**3<sup>rd</sup> LERNER DECLARATION UNDER 37 C.F.R. 1.132**

I, Adam Lerner, M.D., pursuant to 37 C.F.R. § 1.132, hereby declare that:

1. I am an Associate Professor of Medicine in the Section of Hematology/Oncology at Boston Medical Center, Boston University. A true copy of my CV has been submitted with the Amendment filed on April 25, 2008.
2. I am the sole inventor of the above-described application.
3. I have been advised that in the July 18, 2008 Office Action, the Examiner asserted that “no evidence has been submitted that the ‘PDE4 inhibitors’ known in the art do not inhibit Type 1 or Type 3 PDEs at all or only have background level inhibition of such enzymes.” (Page 4, lines 22-24 of the Office Action dated July 18, 2008). Thus, the Examiner appears to question whether the term “specific” or “selective” in the prior art really means “specific” and not “preferential” or “non-specific.”
4. I respectfully submit that, as was clear to the skilled artisan at the time of filing, the term “specific” used in the art at the time the application was filed referred to a truly “specific” PDE4 inhibitor and not an inhibitor that would have also inhibited other PDEs, even if it inhibited PDE4 more.
5. I herewith point to further evidence that the general knowledge in the art regarding non-specific PDE inhibitors and PDE inhibitors with specificity to a class of PDEs, such as inhibitors that specifically inhibit PDE4, was such that there was no ambiguity with

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respect to the compounds that form the class of compounds referred to as “specific PDE4 inhibitors.”

6. As stated in my 2<sup>nd</sup> Declaration (par. 8), prior to the filing date of the present application, i.e. prior to September 24, 1998, the term “specific PDE4 inhibitor” was well known: A number of other specific PDE4 inhibitors were well known to a skilled artisan. For example, compounds RP73401, LAS31025, SB207499, and CDP840, CP80633, CP77059BRL61063, denbufylline, and MNS949 were all **known to the skilled artisan as specific PDE4 inhibitors** (see, e.g., review by Teixeira et al. Trends in Pharm. Sci. 18:164-71, 1997, Exhibit B submitted on April 25, 2008, and Cooper et al. British Journal of Pharmacology, 126:1863-1871, 1999, Exhibit C submitted on April 25, 2008). These inhibitors specifically only inhibited PDE4 and not other PDEs.
7. It has further been well known since the 1970’s that different forms of PDEs can be differentially and selectively, i.e. specifically, inhibited with pharmacological agents (see, e.g., p. 21, col. 1, Lerner and Epstein, Biochem J 393:21-41, 2006, Exhibit G submitted on April 25, 2008).
9. Methods for determining specific PDE inhibiting activity were well known to the scientists at the time the present application was filed.
10. The distinction between a non-specific and “specific”, also synonymously called “selective”, PDE inhibitor was also well known to the scientists at the time the present application was filed (see, e.g., abstract of Holbrook M, Coker SJ., Br J Pharmacol. 1989 Sep;98(1):318-24, wherein the aim of the study was to compare the effects of the non-selective phosphodiesterase (PDE) inhibitor, isobutylmethylxanthine (IBMX) and the selective PDE III inhibitor, milrinone, in a rabbit model of acute myocardial ischaemia, attached herewith as Exhibit H).
11. Also Teixeira makes a clear distinction between non-specific PDE inhibitors, such as theophylline, and inhibitors that are specific to a particular PDE, such as PDE4 inhibitors, like rolipram, RP73401, SB207499, LAS31025, and CDP840 (see, e.g., page 169 col. 1, lines 1-13, and col. 2, under Concluding remarks of Teixeira, Exhibit B). It is clear from Teixeira that referring to “PDE4 inhibitors”, he means “specific PDE4 inhibitors”, i.e. inhibitors that specifically inhibit PDE4 and not other PDEs because inhibitors that are not specific are referred to as “non-specific PDE inhibitors.” This distinction in the definition is also clear throughout the literature discussing PDE inhibitors (see, e.g., the

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review article by Boswell-Smith et al., British Journal of Pharmacology, 147(S1), 2006, attached herewith as Exhibit I).

12. In implying that the class of specific PDE4 inhibitors is not a known class of inhibitors that specifically inhibit PDE4 and not other PDEs, the Examiner is simply wrong.
13. In developing new “specific PDE inhibitors”, one naturally has to determine if they are “specific” to a PDE one wishes to inhibit.
14. A skilled artisan knew how to perform tests to show PDE4 specificity of any inhibitory compound.
15. My understanding is confirmed by Trifilieff, which shows an analysis of several different specific PDE4 inhibitors and their effect on various PDEs using well known techniques (The Journal of Pharmacology, 301:241-248, 2002, attached herewith as Exhibit J).
16. Trifilieff's data also unequivocally confirms PDE4 specificity of four different “specific” PDE4 inhibitors, including NVP-ABE171, Ariflo, V11294A and LAS 31025 (see, Table 1 at page 243, Id., data showing effect on PDE4, PDE1, PDE2, PDE3 and PDE5).
17. In addition, Aoki et al. confirms that specific PDE4 inhibitors YM976, Rolipram, RP73401, SB207499, and CDP840 also had no effect on PDE1, PDE2, PDE3 or PDE5 (see Table 1, page 275, in Aoki et al., The Journal of Pharmacology, 295:255-260, 2000, attached herewith as Exhibit K, showing IC<sub>50</sub> values of various specific PDE4 inhibitors in PDE4, PDE2, PDE3, and PDE5).
18. I taught that the class of such specific PDE4 inhibitors could be used in methods for treating CLL.
19. Accordingly, based both on the specification and the general knowledge in the art prior to September 24, 1998 the skilled artisan was in possession of a broad class of compounds defined as “specific PDE4 inhibitors.”

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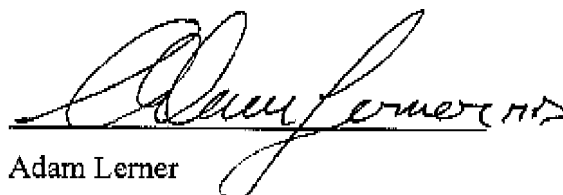
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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

January 15<sup>th</sup>, 2009

Date



Adam Lerner